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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/788,466	03/01/2004	Steven Louis Shafer	44893-0004	9229

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RIDOUT & MAYBEE
SUITE 2400
ONE QUEEN STREET EAST
TORONTO, ON M5C3B1
CANADA

EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	**PAPER NUMBER**
1616	

DATE MAILED: 07/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/788,466	SHAFER ET AL.	
	Examiner	Art Unit	
	James H. Alstrum-Acevedo	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) *37-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/6/04;7/5/05;*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-47 are pending. Receipt and consideration of Applicants' arguments/remarks in response to the restriction requirement submitted on June 23, 2006 is acknowledged. Claims 37-47 are withdrawn from consideration. **Claims 1-36 are under consideration in the instant office action.**

Election/Restrictions

Applicant's election with traverse of Group I (Claims 1-36) in the reply filed on June 23, 2006 is acknowledged. The traversal is on the ground(s) that (a) the product as claimed cannot be used in an alternative method (e.g. in a method treating heroin addiction); (b) a pulmonary delivery device as claimed cannot be used in a method of treating respiratory diseases; (c) the subcombination (i.e. kit) as claimed does not have separate utility such as in the parenteral or orally delivery of a medical formulation. This is not found persuasive because the four groups represent patentably distinct subject matter as evidenced by the differing classifications of said groups. Furthermore, it is noted that a method of administration is patentably distinct wherein the steps of administration distinguish it over the prior art methods; a pulmonary delivery device is patentably distinct wherein its functional working components distinguish it over prior art pulmonary devices, not based upon the contained formulation (all pulmonary delivery devices are inherently containers); and kits comprising an opioid formulation can be used in methods requiring parenteral/oral administration.

The requirement is still deemed proper and is therefore made FINAL.

Claims 37-47 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on June 23, 2006.

Specification

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

The use of the trademark STELLA® ([0036], [0038], [0040]-[0047], [0050], [0101]-[0107], and [0109]-[0113]), has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-16, 18-20, and 22-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Mezei et al. (U.S. Patent No. 5,451,408).

Applicant claims an opioid formulation comprising at least one rapid onset opioid, selected from fentanyl, alfentanil, sufentanil, and remifantanil. The intended use any

limitations associated with the intended use of the claimed compositions were given no weight in the examination of the instant application.

Mezei discloses **liposome-encapsulated opioid analgesic agents delivered by the pulmonary route** provide local, or systemic analgesia superior to that produced by the solution form of these agents administered by parenteral (intravenous, intramuscular, or subcutaneous injection) or oral routes (abstract). The inhalation of liposome-encapsulated opioid analgesic agents offers the following benefits as a method of analgesic drug administration: (1) a simple and noninvasive route of administration; (2) a **rapid onset of analgesia** from absorption of free opioid (in **the range of 10-20% of the opioid dose**); (3) a **sustained analgesia** from continued release of liposome-encapsulated opioid (**approximately 80-90% of the opioid dose**) and (4) a low cost. The sustained release property of the liposomal product can be regulated by the nature of the lipid membrane and by the inclusion of other excipients in the composition of the liposomal products (col. 3, lines 60-63; col. 4, lines 12-15, 18-27). Mezei's liposome-encapsulated opioid analgesic agents can be delivered by direct inhalation of an aerosol using any of the variety of known methods for delivering drugs through the pulmonary system. Representative active ingredients include **fentanyl, alfentanil, sufentanil and morphine** (col. 5, lines 45-50 and 64-66). Mezei exemplifies compositions comprising **fentanyl citrate, alfentanil HCl, sufentanil, and morphine** in Examples 1-8, wherein each example formulation is representative of a 100 ml sample. Example 2 discloses a composition comprising 60 mg of fentanyl citrate in 100 ml water (600 micrograms of total opioid/ml; 60-120 micrograms of free fentanyl; and 480-540 micrograms of liposomally encapsulated fentanyl). It is the Examiner's position that the compositions

disclosed by Mezei inherently yield a maximum opioid plasma concentration at the onset of side effect that is no less than 66% of the maximum opioid plasma concentration, because the amounts of opioid disclosed by Mezei overlap with the ranges claimed by Applicant.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue; and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17, 21, and 29-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mezei et al. (U.S. Patent No. 5451408).

Applicant Claims

Applicant claims an opioid formulation comprising at least one rapid onset opioid, selected from fentanyl, alfentanil, sufentanil, and remifantanil, and at least one sustained-effect opioid, selected from morphine, morphine-6-glucuronide, methadone, hydromorphone, meperidine, an opioid encapsulated in a biocompatible carrier, and a liposomally encapsulated opioid, wherein (a) the ratio of free fentanyl to liposomally encapsulated fentanyl is about 1:3; (b) wherein the formulation consists of alfentanil and morphine; or (c) the formulation contains alfentanil in a concentration from 300-6700 mcg/ml and morphine in a concentration of from 650-13,350 mcg/ml. The intended use any limitations associated with the intended use of the claimed compositions were given no weight in the examination of the instant application.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Mezei have been set forth above.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Mezei does not anticipate the claims cited in the instant rejection, because Mezei lacks the explicit teaching of (a) a ratio of free fentanyl to liposomally encapsulated fentanyl is about 1:3; (b) a formulation consisting of alfentanil and morphine; and (c) a formulation containing alfentanil in a concentration from 300-6700 mcg/ml and morphine in a concentration of from 650-13,350 mcg/ml.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to modify the teachings of Mezei to utilize a ratio of about 2:3 of free fentanyl to liposomally encapsulated fentanyl, because Mezei's compositions inherently comprise free fentanyl and liposomally encapsulated fentanyl in a ratio ranging from 1:4 to about 1:9. The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient needed to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of ingredient amounts would have been obvious at the time of applicant's invention. Regarding the amounts of alfentanil and morphine, Mezei teaches exemplified compositions comprising 2,000 mcg/ml and 4,000 mcg/ml, respectively. The motivation to combine alfentanil and morphine comes from the prior art. It is generally considered *prima facie* obvious to combine two compounds

each of which is taught by the prior art to be useful for the same purpose, in order to form a composition which is to be used for the very same purpose. The idea for combining them flows logically from their having been used individually in the prior art. See *In re Kerkhoven*, 626, F.2d 848, 205 USPQ 1069 (CCPA 1980). As shown by the recited teachings, the instant claims define nothing more than the concomitant use of two known opioid analgesic agents. It would follow that the recited claims define *prima facie* obvious subject matter. For the aforementioned reasons, a person of ordinary skill in the art would have had a reasonable expectation of success upon modification of the ratio of free fentanyl to liposomally encapsulated fentanyl as well as modification of opioid compositions to comprise both alfentanil and morphine.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 5-18 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 10-25 of U.S. Patent No. RE38407. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are substantially overlapping in scope and mutually obvious. The cited claims of RE38407 claim a method of managing pain (i.e. analgesia) comprising the administration of a liposome-encapsulated opioid analgesic and/or in admixture with a non-encapsulated opioid, such as fentanyl, alfentanil, sulfentanil, and both free fentanyl/liposome encapsulated fentanyl. The compositions utilized in the method of RE38407 are obvious over the claimed compositions of the instant application.

Claims 1, 5-11, 13-21, 29-30, and 33 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 and 48 of copending Application No. 10/927,145 (copending '145). Although the conflicting claims are not identical, they are not patentably distinct from each other because they are substantially overlapping in scope and mutually obvious. The cited claims of the instant application and copending '145 both claim opioid formulations comprising at least one rapid-onset opioid and at least one sustained-effect opioid, wherein the opioids consist of, for example, fentanyl and liposomally encapsulated fentanyl. Both applications claim overlapping and/or mutually obvious ratios of fentanyl to liposome-encapsulated fentanyl, total opioid concentration, and overlapping Markush groups of both rapid onset and sustained-effect opioids.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Krugner-Higby et al. (US 2003/0157162) is pertinent art, because it teaches liposome-encapsulated opioid analgesics, wherein the opioid includes morphine, hydromorphone, butorphanol, or oxymorphone.

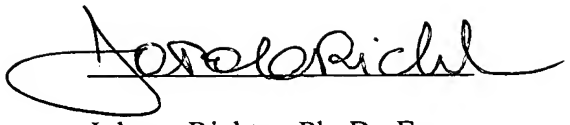
Claims 1-36 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, 9:00-6:30, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0664. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

James H. Alstrum-Acevedo, Ph.D.
Patent Examiner
Technology Center 1600



Johann Richter, Ph. D., Esq.
Supervisory Patent Examiner
Technology Center 1600